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Physiological effects of low-magnitude electric fields on brain activity: advances from *in vitro*, *in vivo* and *in silico* models

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Abstract

While electrical stimulation of brain tissue has been thoroughly investigated over the last decades, ongoing questions remain regarding the neurophysiological effects of low-level electric fields (on the order of 1 V/m) on brain activity. Electric fields at such levels are, for example, induced by transcranial direct/alternating current stimulation (tDCS/tACS). Action potentials can be indeed elicited when applied (supra-threshold) electric fields are in the 10–100 V/m range, while lower (subthreshold) electric fields result in more limited and subtler membrane polarization effects. In this review, we address the question of the mechanisms underlying the immediate effects (also referred to as acute, concurrent or short-term) and the lasting effects (also referred to as long-term or aftereffects) of low-level electric fields on brain tissue. We review recent evidence at the *in vitro* and *in vivo* (animal and human) level, and also present mechanistic insights gained from *in silico* models, which are still few but have received increased attention over the recent past years. We highlight the convergent evidence towards potential mechanisms, and also discuss discrepancies between *in vitro* studies and human tDCS/tACS studies that require further investigation to bridge the gap between the single-cell and large-scale network level. Possible novel avenues of research are discussed.

Keywords

Electric fields; transcranial direct current stimulation (tDCS); transcranial alternating current stimulation (tACS); electrophysiology; *in vitro*; *in vivo*; computational; model

1. Introduction

Electrical stimulation has established as a standard clinical practice in a number of clinical applications, ranging from diagnostic (e.g., functional stimulation during stereoelectroencephalography -SEEG- in drug-refractory epileptic patients) to therapeutic (e.g., chronic stimulation of deep brain regions in Parkinson's disease to alleviate motor

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Disclosure

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symptoms) procedures. A common point of these applications of electrical stimulation is that they are based on the use of *suprathreshold* electric fields, i.e. electric fields that are sufficiently strong to trigger action potentials at the level of single cells. However, increasingly popular neuromodulation techniques such as transcranial current stimulation (tCS) are based on the use of electric currents (typically up to 2 mA), either direct (tDCS) or alternating (tACS), delivered at the level of the scalp. Effects of transcranial electrical stimulation depend on the surface area of the stimulating electrodes. Since current density corresponds to the (stimulation strength (A)/electrode size (cm²)) ratio, tDCS electrodes/wet sponges used in human with a nominal size of 25–35 cm² and currents of 2 mA result in current densities on the order of ~0.01–0.05 mA/cm² (Nitsche et al., 2003; Thair et al., 2017). The fraction of current reaching the cortex also depends on the electrode placement as shown by pioneer work of (Rush and Driscoll 1968). For instance, for bipolar electrodes positioned on the centers of the occipital and frontal bones, the total current passing through the cranial cavity was about 45% of that applied. For an electrode spacing less than 5 cm, the shunting effect of the skull and cerebrospinal fluid -CSF- predominates. tCS exerts multiple effects on brain tissue activity, with detectable effects at the behavioral and/or clinical level. While conflicting data exists in the literature on the consistency of these effects, there is now converging evidence that the electric fields induced by tDCS/tACS, even if subthreshold (on the order of 1 V/m, Fig 1A), can modulate neuronal function. In particular, it is estimated that a tDCS intensity of 1 mA generates electrical fields at the level of cortical neurons in the 0.2–0.5 V/m range (Miranda, Lomarev et al. 2006, Datta, Bansal et al. 2009, Sadleir, Vannorsdall et al. 2010), while 2 mA (~0.01mA/cm²) would produce an electric field of about 1 V/m (Jackson, Rahman et al. 2016, Voroslakos, Takeuchi et al. 2018). Interestingly, for those values (tDCS at an intensity of 2 mA generating an electric field of 1 V/m), the voltage gradient on the neuronal resting membrane potential is estimated on the order of 0.2 mV (Bikson, Inoue et al. 2004), a value far from being able to bring neurons to spiking threshold.

Therefore, the main question that arises is: what are the mechanisms that explain neurophysiological effects, for such levels of *in situ* electric field? Among the reported effects of induced electric fields in humans, the most reproducible effect at the lowest known electric field levels (< 0.1 V/m *in situ* at 20 Hz, (IEEE 2010, International Commission on Non-Ionizing Radiation 2010, Hirata, Takano et al. 2011, Laakso and Hirata 2012)) is the perception of electro- and magneto-phosphenes, consisting in the perception of flickering lights due to the currents induced in the brain, and most certainly within the retina (Lovsund, Oberg et al. 1980, Attwell 2003). However, the retina has a very specific architecture adapted for the amplification of weak signals (e.g., convergent pathways between photoreceptors and bipolar cells (Attwell 2003)), which cannot directly be translated to the rest of the brain. A considerable number of studies have therefore attempted to investigate the question of interaction mechanisms of electric fields in the 1 V/m range, from cultures of cells (*in vitro*) to animal experiments (*in vivo*). Significant efforts have also been done in the field of computational modeling (*in silico*) to integrate these experimental results. Therefore, in the following, we focus on the main results on the exploration of interaction mechanisms, approached with experimental and modeling techniques. Furthermore, for each level of description, we mention the results that have been obtained both in terms of *acute* and

lasting effects. By “acute”, we refer to immediate effects occurring concurrently with tCS (i.e during stimulation) or on the short term (i.e seconds after stimulation) while the terminology “lasting” refers to after-effects observed on a longer term (i.e. hours or days after stimulation).

2. *In vitro* approaches

Most *in vitro* studies have been performed using an experimental setup consisting of two long parallel wires or plates placed in the bath where hippocampal or cortical slices are maintained. The major advantages of this specific setup are the generation of a quasi-uniform electric field across the entire tissue, and the possibility to measure (e.g., patch clamp) the impact on cellular properties for different DC stimulation parameters. In this setup, the effects on neurophysiology are strongly dependent on the electric field orientation and stimulation intensity (Fig 1A), as mentioned in (Kabakov, Muller et al. 2012) and (Rahman, Reato et al. 2013). Among the numerous effects reported *in vitro*, a number of significant modifications have been reported: in calcium entry, depolarization, hyperpolarization, firing rate, spike timing, neuronal input/output function, modulation of synaptic transmission, modulation of NMDA-dependent long-term potentiation, modulation of mGluR-dependent long-term depression (Sun, Lipton et al. 2016) and even morphological changes such as axonal growth and guidance (Jackson, Rahman et al. 2016, Kronberg, Bridi et al. 2017, Lafon, Rahman et al. 2017).

However, one major drawback of most DC stimulation *in vitro* studies is that they involve electric field magnitudes of 20 to 60 V/m, which is at least 20 times higher than the electric field induced in the human brain for a 2mA tDCS (~1 V/m). It is worth noting though that no proper modeling of the whole experimental setup (slice and recording chamber filled in with ACSF), including electric fields induced in the depth of the slice, has been reported so far and actual values are likely lower. Therefore, the direct correspondence between these *in vitro* results and the neurophysiological mechanisms triggered by non-invasive electrical brain stimulation (which involves much weaker *in situ* fields) is not obvious. Furthermore, one should mention that, in the highly folded human brain cortex, tDCS-induced electric fields generated by two or more distant electrodes is not uniform. This limitation was addressed in a few *in vitro* studies which made use of more realistic tDCS/tACS-level electric fields (0.5 to 1 V/m) stimulation. Results confirmed an average of 0.12 mV depolarization of the cell bodies for each 1 V/m of applied field (Jefferys, Deans et al. 2003), and a modulation of axon terminals polarization that are two–three fold more sensitive than somas (Reato, Rahman et al. 2010). While the impact of electric fields of such magnitude on single neuron activity is almost negligible, the situation might be different at the level of local neural networks involving several thousand neurons. One of the possible mechanisms of tDCS might indeed be the network-wide amplification of weak membrane depolarizations (Frohlich and McCormick 2010), as illustrated by computational simulations in Fig 1B. Since tDCS impacts mainly axon terminals, and since neurotransmitter release is very sensitive to presynaptic bouton polarization (Debanne, Campanac et al. 2011), the main effect of tDCS might actually be on synaptic transmission (Fig 1C) and presynaptic modulation of short-term plasticity (Rahman, Lafon et al. 2017), even if such mechanisms remain to be demonstrated for an electric field on the order of 1 V/m. Finally, one drawback

of most of these experiments is the lack of a corresponding computational model that would account for several factors, among which the relative orientation between the electric field and neurons, the differential effect of the electric field on specific locations of neuronal complex geometry. Therefore, conclusions from these studies have to be taken with caution, since the interplay between electric fields and neuronal type and geometry can greatly affect the outcome.

3. *In vivo* approaches

In vivo experiments can highlight some after-effects of tDCS on longer time scales (days) as compared to *in vitro* studies (hours). As aforementioned, network-based mechanisms might be one fundamental mechanism of tDCS-level electric fields. Therefore, it is required to analyze the response of brain tissue with intact connectivity to such fields, which has been the motivation in a number of recent *in vivo* studies, mostly conducted in rodents. It has been shown that transcranial current anodal stimulation in mice could facilitate memory (preference towards novel objects), an effect that persisted one week after stimulation and likely explained by increasing hippocampal long-term plasticity.

Glutamatergic circuits seems to be particularly affected by direct current stimulation. NMDA receptor dependent long-term synaptic potentiation (LTP) (Fritsch, Reis et al. 2010) and AMPA receptor translocation and phosphorylation (Stafford, Brownlow et al. 2018) can be induced by direct current stimulation *in vivo*.

Interestingly, blockade of the TrkB brain-derived neurotrophic factor (BDNF) receptor reduced tDCS facilitating effects on memory and tDCS-induced long-lasting changes in BDNF expression by epigenetic mechanisms (Podda, Cocco et al. 2016), suggesting that tDCS might have, at least indirectly, effects on BDNF regulation. Inversely, long-term depression (LTD) evoked in the somatosensory cortex behaving rabbit after cathodal tDCS is prevented by adenosine A1 receptors blockade, suggesting that tDCS might influence adenosine release in glutamatergic circuits (MarquezRuiz, Leal-Campanario et al. 2012).

Another possible mechanism of tDCS is the indirect neuromodulation of cortical circuits through astrocytes. Even if this glial cell type is not excitable *per se*, and the membrane potential is stable, it seems sensitive to electric fields. Among the reported effects, increased glucose metabolism was found in cultured cortical mouse astrocytes under low magnitude electric fields (0.3 V/m) induced by tDCS (Huang, Peng et al. 1997). Recent studies using the calcium indicator G-CAMP7 expression in mice astrocytes *in vivo*, pointed at the indirect activation of astrocytic networks by tDCS, through the release of neurotransmitters such as noradrenaline (Monai, Ohkura et al. 2016, Monai and Hirase 2018). Since the activity of glial cells (astrocyte, microglia) interferes with synaptic plasticity, their modulation provides a possible explanation to the well-established lasting effect of tDCS (Gellner, Reis et al. 2016). Interestingly, based on the predictions of a computational model, a recent study (Mina, Modolo et al. 2017), tested experimentally the possibility to modulate epileptic hippocampal paroxysmal discharges (HPDs), which are observed in a mouse model of epilepsy, using DC stimulation delivered intracranially. A drastic reduction of HPDs was observed when anodal stimulation was delivered, generating an electric field on average < 5

V/m in the hippocampus. More specifically, in terms of underlying mechanisms, the model also predicted that the effect was mainly mediated by the depolarization of slow, dendritic-targeting GABAergic inhibitory interneurons, a testable hypothesis.

4. *In silico* approaches

As illustrated by the two previous sections, and despite the many *in vitro* and *in vivo* studies which have been conducted to investigate the behavior of small and large networks of neurons under the effect of electric or magnetic stimulations, the mechanisms by which low-level E-fields (i.e. compatible with those induced by tCS) impact the activity of neuronal assemblies remain elusive, as is the link between immediate and after-effects. In this context, *in silico* models also constitute a promising - though probably more challenging - approach to quantitatively analyze and predict the impact of direct or alternating stimulation currents (intensity, frequency, duration, repetition) and resulting fields (distribution and orientation w.r.t. neurons) onto brain systems. In this section, we review some recent attempts (5 past years) to model the coupling between exogenous E-fields and neuron membranes as well as attempts to describe subsequent short-term (polarization-related) and long-term (plasticity-related) effects.

Regarding acute effects at single cell level, the classical theoretical framework to describe transmembrane potential changes generated by exogenous E-fields is provided by the cable theory (Rall 1959) also referred to as the Goldman–Hodgkin–Huxley–Katz model (GHHK) (Fig 1D). Recently, Wang et al. (Wang, Aberra et al. 2018) revisited the cable equation (CE) in order to better capture the mutual interactions between the applied field and neuron membrane polarization. Starting from previous work (Krassowska and Neu 1994), they derived new equations describing the two distinct time scales of cell membrane changes in response to an imposed extracellular E-field. Specifically, their model now accounts for initial polarization, a fast response due to transverse polarization (TP) in addition to the slower change in the mean membrane potential accounted for by the classical CE. Interestingly, authors emphasize the potential benefit of the modified CE i) in situations involving low spatial gradient of E-fields and ii) for modeling of the network behavior in response to TP-induced subthreshold modulation. A second interesting modeling study is that reported by Lafon et al. (Lafon, Rahman et al. 2017) who made use of a computational neuron model to analyze the alteration of the input(synaptic)–output(spiking) function achieved by direct current stimulation (DCS). Starting from a reduced two-compartment pyramidal cell model based on Hodgkin–Huxley formalism for active conductances, results show that a leftward shift in the input–output threshold under anodal stimulation which leads to membrane hyperpolarization at the dendrites concomitantly with depolarization at the soma. Results also suggest that synergetic interactions between the two compartments is crucial for describing the effects of DCS at cellular level. Finally, it is worth mentioning that the GHHK theory assumes ionic homogeneity and thus breaks down for small neuronal compartments such as dendritic spines or synaptic terminals that are likely impacted by weak E-Fields. Readers may refer to a broader theory based on Poisson–Nernst–Planck (PNP) approximation to more accurately account for electrodiffusion and in neuronal nanostructures (review in (Holcman and Yuste 2015)).

So far, only few studies have addressed the modeling of acute effects of low-magnitude E-fields at the neuronal population level. One study attempted, using the neural mass formalism, to describe the impact of the electric field induced by tDCS on evoked brain responses (Molaei-Ardekani, Marquez-Ruiz et al. 2013). Using the “lambda-E” model {Ruffini, 2013 #44} inspired by earlier *in vitro* work, a model featuring pyramidal cells, slow and fast GABAergic interneurons, was used to fit airpuff evoked responses in the rabbit somatosensory cortex (Marquez-Ruiz, Leal-Campanario et al. 2012). Different physiological mechanisms were tested, and the optimal fit between simulated and experimental evoked responses was obtained for a depolarization of pyramidal cells and slowkinetics interneurons (SOM+) combined with a hyperpolarization of fast-kinetics interneurons (basket cells). Interestingly, this modeling study emphasizes that low-magnitude electric fields as induced by tDCS interact with all types of neurons and have differential effects depending on their typology and orientation in the cortex. Future computational studies should also explore possible synapseindependent ephaptic effects (Anastassiou, Perin et al. 2011) according to which “tDCS-activated” neurons generate electric field interactions with neighbor (i.e. juxtaposed) “passive” neurons (Fig 1D). Such interactions were hypothesized to reinforce synchronization of neuronal activity and thus impact information processing and plasticity in the brain.

Finally, long-term effects induced by tDCS-level electric fields are a topic of outmost importance, especially in the context of neurological disorders like epilepsy where long-lasting “protective” (i.e. aimed at reducing cortical excitability) effects should be maximized. Among the limited number of studies reported so far, one can quote the neural mass model proposed by Modolo et al. (Modolo, Thomas et al. 2013) featuring a simplified calcium-dependent synaptic plasticity mechanism, supported by the evidence that post-synaptic calcium concentration regulates the trafficking of AMPA receptors (Shouval, Castellani et al. 2002). In this model, post-synaptic calcium concentration was expressed as a low-pass filtered version of the EEG, with a time constant derived from experimental values for calcium concentration changes (Manahan-Vaughan, Kulla et al. 2000). Testing different scenarios for the possible physiological targets of the induced electric field, it was shown that levels of membrane depolarization on the order of 0.5 mV could be sufficient to induce significant modulations of alpha power in simulated EEG signals.

5. Conclusion

The multitude of neurophysiological effects reported by the use of low-magnitude electric fields (on the order of 1 V/m) has sparked a significant interest due to its outstanding potential to offer novel non-invasive therapies for neurological disorders. However, the critical review of this literature highlights some crucial points, that should be carefully addressed in future studies tackling this question, not only to improve the interpretation of results in this research field, but also to bridge the gap between *in vitro/in vivo* data and reported behavioral effects. First, a systematic dosimetry of the electric field delivered within each experimental setup should be systematically provided as a good practice. Failing to provide such information might complicate the comparison between studies, and induce confusion regarding the possible targets and mechanisms. Second, the order of magnitude of the electric field used *in vitro* should be as close as possible to the fields induced by tDCS/

tACS, in order to provide meaningful insights into the results obtained clinically. One problem is indeed that most *in vitro* studies investigating interaction mechanisms use electric fields that are 10 to 100 times higher than those generated by tCS. Third, combined *in vivo/in silico* studies should be encouraged as an attempt to validate candidate interaction mechanisms, which could then be exploited to unleash the full potential of tDCS/tACS for therapy. Finally, while neurons appear as the most likely candidate to explain the effects of low-level electric fields, it might be time to explore beyond this paradigm to consider potential effects on astrocytes or microglia. While experimentally challenging, this might prove extremely fruitful to reach a proper understanding of the involved phenomena.

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Figure 1.

A: Effects of transcranial low-level electric fields depends on cortical neuron orientation and brain geometry, but 1 mA generates electrical fields $< 1 \text{ V/m}$ and induce very limited polarization effect on the resting membrane potential. The right panel illustrates the orientation of cortical neurons apical dendrites perpendicular to the gyri surface (photography from the cortex of GFP-transgenic mice) and superimposed to the theoretical electric field.

B: Computational illustration of the network-wide amplification of weak (sub-threshold) field effects under anodal tDCS.

B1: A detailed computational model (unpublished) comprising 100 000 synapses connecting 1000 neurons (principal neurons and GABAergic interneurons (i.e. basket, somatostatin-positive -SST-, vasoactive intestinal polypeptide-positive -VIP-). tDCS modulates neurotransmission by slightly modifying the probability of release and post synaptic potential of each individual synapse, depending on its position in the electric field.

B2: In the model presented in (B1), simulated tDCS does not affect the neurophysiological properties of an isolated cortical pyramidal cell. This illustration shows that the firing pattern of an individual neuron does not change without (top) or in the presence (bottom) of simulated tDCS effects.

B3: In the same configuration than (B2) in the absence of visible effects on a single neuron, tDCS induces a network modulation. *Left.* Superimposed firing patterns of 1000 neurons are shown (red traces: pyramidal neurons; green: basket cells; blue : SST interneurons; yellow : VIP Interneurons) in absence (top) or presence (bottom) of simulated tDCS. Intra = simulated intracellular recording of individual neurons. The corresponding simulated local field potential (LFP) is depicted in gray upon individual traces. Note that, in the presence of simulated tDCS, the synchronization pattern of the neural network LFP changes as shown in the respective power spectrum (*right*). a.u: arbitrary unit. PSD: Power spectrum density.

C. Illustration of transcranially-induced weak fields slightly polarizing axon terminals and modulating synaptic transmission. Note that presynaptic synapses compartments are not uniformly oriented. Transcranial current stimulation might also affect glial cells such as astrocytes (grey).

D. Synthetic view on the effects of exogenous and endogenous fields. A positive electric field is oriented along decreasing potentials (grey arrow, positive $E_{EXO} > 0$). A tDCS-range exogenous field has minor effects on neuronal activity and excitability. In the opposite direction (red arrow, negative field $E_{EXO} < 0$), the field may slightly depolarize the soma (close to the anode) and hyperpolarize the apical dendrite due to induced currents flowing across the transmembrane resistance. Excitability is increased in this case. In addition, impacted neurons create themselves an endogenous field (blue arrow, E_{ENDO}) that will also influence passive neighbouring neurons (illustrated on the right as a passive neuron). Such possible ephaptic interactions possibly contribute to changes in excitability and synchronization at the network level. VTM=transmembrane membrane potential. I = current. Adapted from *Brain Stimulation: models, experiments and open questions*; **DELIVERABLE D1.1: Review of state-of-the-art in currents distribution and effects, Hive Project**, EU FP7 FET OPEN – 222079, 2009.